Support for Amendments

Applicants have amended claim 8 to specify that the AGE-1 DNA is isolated and is at least 95% identical at the amino acid level to SEQ ID NO: 1. These amendments find support throughout the specification, for example, at page 5, lines 19-20; page 13, lines 11-12; page 20, lines 7-17; and page 26, lines 12-14. In addition, claim 19 has been limited to nematode systems, an amendment that finds support, for example, at page 31, line 14. All other amendments serve merely to conform the dependent claims with these revisions to claim 8 or to clarify claim language. No new matter is added by these amendments.

The present amendments were made solely to expedite allowance of claims in this case, and should not be construed in any way to indicate that applicants agree with the current rejections. Applicants fully intend to pursue the canceled subject matter in future related applications, and reserve their right to do so.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 8-11 and 29-30 stand rejected, under 35 U.S.C. § 112, first paragraph, based on the assertion that the claims contain subject matter that does not satisfy the written description requirement, as set forth in the PTO interim guidelines.[1] As applied to

[1] Claim 13, while not expressly rejected, is mentioned in the text associated with the written description rejection. Applicants request clarification of this point in the next Action and direct the Examiner to the amendment of claim 8 (which is referred to in

the current claims, this rejection is respectfully traversed.

Amended claim 8, on which the remaining claims depend, is directed to DNAs that encode AGE-1 polypeptides that are at least 95% identical to SEQ ID NO: 1. In addition, these encoded polypeptides are required to exhibit PI 3-kinase activity and to include p85-binding and lipid kinase domains, structural features that are responsible for such kinase activity. These claims are entirely consistent with the written description guidelines set out by the Patent Office and more than satisfy the Office's concerns regarding the amount of identity and structural features necessary for AGE-1 polypeptides to act as PI 3-kinases.

In addition, the Office has focused on the term "substantially pure" and questioned whether applicants' specification provides a written description for this term. While applicants submit that the term is fully disclosed and even defined in the specification, this term is no longer included in claim 8, and this basis for the rejection is therefore moot. The written description rejection may be withdrawn.

In addition, claims 8-13 and 15-20 stand rejected as lacking enablement. This rejection turns on the assertion that the full scope of AGE-1 nucleic acids previously claimed would not be expected to encode polypeptides exhibiting PI 3-kinase activity. While applicants strongly disagree with this assertion, they direct the Examiner's

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claim 13) and applicants' reasons for the withdrawal of this rejection as applied to claims 8-11 and 29-30.

attention to the present claim amendments. These claims, in addition to requiring that the nucleic acids encode polypeptides having PI 3-kinase activity, also require that these polypeptides exhibit at least 95% amino acid sequence identity to SEQ ID NO: 1 and the presence of two domains central to PI 3-kinase function, the p85-binding and lipid kinase motifs.

Despite the concerns expressed by the Office, there is in fact no reason to believe that such polypeptides do not possess PI 3-kinase activity. First, while it is true that AGE-1 represents a divergent class of PI 3-kinases that exhibit relatively low overall sequence identity to their closest relatives, the mammalian p110 kinases, it is also true that AGE-1 proteins possess lipid kinase and p85-binding motifs — structural features that are characteristic of the p110 family. In addition, the Office is directed to page 22, lines 18-20 of the present specification. There, applicants state that, despite the divergence of AGE-1 from the p110 proteins and the resultant decrease in sequence identity, the random probability of alignment of AGE-1 with p110 kinases is extremely low. Specifically, the application notes that the probability of random alignment of AGE-1 with p110α is e^{-113}, with p110β is e^{-101}, and with p110γ is e^{-93}, values that can be compared with the significantly higher probabilities of random alignment, for example, with PI 4-kinases or DNA repair kinases of e^{-22} and e^{-8}, respectively. These probability statistics demonstrate that the somewhat lower overall sequence identity between AGE-1 and mammalian PI 3-kinases is of little importance due to the extremely low likelihood of a

random, erroneous sequence alignment.

Moreover, on the issue of whether AGE-1 would be considered by those of skill in the art to encode a PI 3-kinase, applicants further direct the Examiner's attention to the attached publication by Morris et al. (Exhibit A). This scientific reference from the inventors parallels the results and conclusions contained in the present specification. In particular, the reference describes AGE-1 and states that, due to its homology with p110 enzymes and their shared motifs, AGE-1 is believed to encode a PI 3-kinase. This reference directly addresses the Office's concerns on this point because it demonstrates that these results were peer-reviewed by some of the top scientists in this area of research and published in Nature, one of the most prestigious journals available for the reporting of molecular biology results. Certainly, if the researchers chosen to review articles for Nature agree with the inventors that AGE-1 nucleic acids encode PI 3-kinase proteins, there can be no question that applicants' specification meets the Patent Office standard for objective enablement.

Finally, on this issue, the Examiner is directed to the attached reference by Babar et al. (Exhibit B), further evidence that AGE-1 polypeptides are PI 3-kinases. In this reference, the authors investigated the effects of a known chemical inhibitor of mammalian PI 3-kinase, termed LY294002. As shown at pages 516-517, administration of this mammalian PI 3-kinase inhibitor to nematodes mimicked the effects of AGE-1 mutations, as measured by dauer formation and thermotolerance as well as life span.

These parallel effects between mutations in AGE-1 and administration of a chemical PI 3-kinase inhibitor further support the role of AGE-1 as a PI 3-kinase protein, and are also indicative of the conservation of these enzymes between mammals and nematodes.

In sum, therefore, applicants have submitted strong evidence that AGE-1 polypeptides have PI-3 kinase activity. First, applicants have shown that these polypeptides are most closely related in sequence to mammalian PI-3 kinases and that their degree of relatedness is statistically significant. Moreover, applicants have identified, in AGE-1 polypeptides, sequence motifs (i.e., lipid kinase and p85-binding motifs) that characterize PI-3 kinases of the p110 family. Finally, applicants have submitted a scientific reference indicating that a loss-of-function mutation in AGE-1 behaves in a phenotypic manner that mimics a known chemical inhibitor of mammalian PI 3-kinase.

Applicants submit that this evidence is more than sufficient to satisfy the requirements of § 112, first paragraph. As stated in the case of *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971), the first paragraph of § 112 "requires nothing more than objective enablement." Indeed, in cases where the Office disagrees with statements presented in an applicants' specification:

> ... it is incumbent upon the Patent Office ... to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

In the present case, the only reason of record given for doubting that AGE-1 is a PI-3 kinase is that mammals have three different PI-3(K) subunits and that these subunits "have different regulators and therefore would have different mechanisms of function" (Advisory Action). This statement, however, is inadequate support for the present rejection. Applicants agree that mammals have multiple PI-3 kinase subunits, but point out that it is quite likely that the function of these three subunits is subsumed by a single AGE-1 PI-3 kinase in nematodes. Moreover, while the mammalian subunits may have different regulators, all three exhibit PI-3 kinase activity. It is therefore unimportant which subunit is most closely related to AGE-1; sequence and structural relatedness of AGE-1 to any one of the mammalian subunits would be indicative of a PI 3-kinase protein.

For all of the above reasons, applicants submit that they have met the requirements of § 112 for claims 8-13 ad 15-20, and reconsideration on this issue is requested.

Finally, with respect to claim 19 and the issue of whether modulatory compounds of AGE-1 could be isolated in an in vivo mouse model, applicants point out that this claim is now limited to nematodes, and this basis for the rejection may be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 8-13, 15-20, and 29-30 stand further rejected, under 35 U.S.C. § 112, second paragraph, based on the assertion that certain claim terms are indefinite.

Specifically, claim 8 stands rejected based on the term "purified DNA." Applicants do not believe that this term is indefinite, as it is explicitly defined at pages 4-5 of the specification. Nonetheless, claim 8 has been amended to state a "purified and isolated DNA," as suggested by the Examiner. Applicants note that the present specification indicates that the term "isolated" describes that level of purity that one skilled in the art typically associates with a cloned piece of DNA. It does not require absolute purity, a standard that is unreasonable in this area of technology. Applicants also note that, despite the Examiner's suggestion, the term DNA "segment" has not been added to claim 8, due to the definition of "purified DNA." This definition makes clear that the AGE-1 gene is a DNA segment in that it is separated from the 5' and 3' contiguous coding sequences with which it is naturally-associated in the genome. Accordingly, to add the word "segment" to claim 8 would confuse, rather than clarify, the claim's meaning.

Claims 15 and 16 are also considered indefinite due to the phrase "a decrease in AGE-1 expression [or activity] identifying a modulatory compound." These claims have been clarified by adding a step of measuring AGE-1 expression or activity following contact with a candidate compound, and then identifying a compound that is capable of decreasing AGE-1 expression or activity by its effects relative to an untreated control. This amendment finds clear support in the specification at pages 31, lines 9-27 and page 32, lines 8-21.

The indefiniteness rejections may be withdrawn.

Conclusion

Applicants submit that this case is in condition for allowance, and such action is respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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MARKED UP CLAIMS

8. (Twice Amended) A purified and isolated DNA which encodes an AGE-1 polypeptide having PI 3-kinase activity, said polypeptide having at least [50%] 95% amino acid sequence identity to the full length polypeptide of Figure 6 (SEQ ID NO: 1) and comprising a p85-binding domain and a lipid kinase domain.

10. (Amended) A vector comprising the purified and isolated AGE-1 DNA of claim 8 [or 9].

11. (Amended) A cell comprising the purified and isolated AGE-1 DNA of claim 8 [or 9].

12. (Amended) A method of producing a recombinant AGE-1 polypeptide, said method comprising the steps of:

(a) providing a cell transformed with the DNA of claim 8 [or 9] encoding an AGE-1 polypeptide positioned for expression in the cell;

(b) culturing the transformed cell under conditions for expressing the DNA; and

(c) isolating the recombinant AGE-1 polypeptide.

15. (Amended) A method of identifying an AGE-1 modulatory compound that is capable of decreasing the expression of an AGE-1 gene, said method comprising the steps of:

(a) providing a cell expressing the AGE-1 DNA of claim 8 [or 9]; [and]

(b) contacting said cell with a candidate compound; and

(c) measuring AGE-1 gene expression in said cell, a decrease in AGE-1 gene expression in said cell following contact with said candidate compound, relative to an untreated cell, identifying said candidate compound as a compound that is capable of decreasing AGE-1 gene expression [a modulatory compound].

16. (Twice Amended) A method of identifying an AGE-1 modulatory compound that is capable of decreasing AGE-1 PI 3-kinase activity, said method comprising the steps of:

(a) providing a cell expressing an AGE-1 polypeptide of claim 8; [and]

(b) contacting the cell with a candidate compound; and

(c) measuring the PI 3-kinase activity of said cell, a decrease in AGE-1 PI 3-kinase activity of said cell following contact with the candidate compound, relative to an untreated cell, identifying said candidate compound as a compound that is capable of decreasing AGE-1 PI 3-kinase activity [a modulatory compound].

19. (Amended) The method of claim 15 or 16, wherein said method is carried out in a nematode [or other animal].

29. (Amended) [A purified DNA which encodes an AGE-1 polypeptide] The purified and isolated DNA of claim 8, wherein said polypeptide comprises [said polypeptide comprising] at least 50% of the following amino acids of Figure 6 (SEQ ID NO: 1): amino acids Gly-32, Leu-73, His-78, Phe-81, Glu-109, Phe-114, Leu-123, Leu-125, Phe-129, Lys-181, Ser-208, Lys-211, Arg-321, Leu-325, Leu-351, Ser-355, Met-373, Leu-381, Leu-393, Thr-432, Tyr-451, Glu-475, Pro-507, Ile-514, Gly-518, Glu-530, Val-538, Leu-582, Tyr-606, Pro-643, Phe-665, Leu-744, Leu-745, Arg-762, Leu-789, Arg-794, Ala-827, Arg-829, Trp-835, Ser-842, Asn-905, Gly-917, Asp-975, Ile-990, Asp-1006, His-1020, Lys-1104, Thr-1105, Gly-1130, Phe-1140, and Lys-1144[, wherein said polypeptide comprises a p85 domain and wherein a lipid kinase domain and wherein said polypeptide has PI 3-kinase activity].

30. (Amended) The purified and isolated DNA of claim 29, wherein said polypeptide comprises an identical amino acid in the equivalent position to Ala-827 of Figure 6 (SEQ ID NO: 1).